

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.

A⁴
C¹
Cont

12 ~~C₁₋₆alkyl-C₃₋₈cycloalkyl, -O-R², -O-C(=O)R², -C₁₋₈alkyl-O-R¹⁰, -C₁₋₈alkyl-O-C(=O)R¹⁰,~~
13 ~~-C₁₋₈alkyl-C(=O)OR¹⁰, -C₁₋₈alkyl-O-C(=O)OR¹⁰, -C₁₋₈alkyl-C(=O)NR¹⁰R¹⁰,~~
14 ~~-C₁₋₈alkyl-NR¹⁰R¹⁰, -C₁₋₈alkyl-NR¹⁰C(=O)R¹⁰, -SR¹⁰, where R² is as described above and~~
15 ~~R¹⁰ is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl,~~
16 ~~C₂₋₈alkynyl, and wherein when two R¹⁰ groups are present they may be taken together to~~
17 ~~form a saturated or unsaturated ring with the atom to which they are both attached;~~
18 ~~each R¹⁴ group is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl,~~
19 ~~C₂₋₈alkynyl, C₃₋₈cycloalkyl, halogen, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH,~~
20 ~~C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, -CN, -NO₂, C₁₋₈alkyl-OH, C₀₋₈alkyl-SH, -O-R² and~~
21 ~~-O-C(=O)R², an unsubstituted amino group, a mono- or di-substituted amino group,~~
22 ~~wherein the substituted amino groups are independently substituted by at least one~~
23 ~~member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl,~~
24 ~~C₃₋₈cycloalkyl, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH and C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl;~~
25 ~~or a pharmaceutically acceptable diastereomer, salt, hydrate, and solvate thereof.~~

REMARKS

Claims 1-16 are pending in this application and presented for examination. Claims 1-2, 5, 9 and 11 have been amended. No new matter has been introduced with the foregoing amendments. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." Reconsideration is respectfully requested.

I. REJECTION UNDER 35 U.S.C. § 112, second paragraph

Claims 1-16 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Each of the Examiner's concerns, and Applicants response to those concerns, will be addressed in turn.

a) With respect to the double inclusion of the variable "OH" in R^1 and R^{14} , Applicants have amended " C_0 - C_6 alkyl-OH" to set forth C_1 - C_6 alkyl-OH. As such, Applicants respectfully request that the Examiner withdraw the rejection.

b) With respect to the typographical errors of r^6 and r^{18} , Applicants have amended the claims to set forth R^6 and R^{18} . As such, Applicants respectfully request that the Examiner withdraw the rejection.

c) With respect to the term "prodrug derivatives", Applicants have deleted the term from the claims in an earnest effort to advance prosecution of the application. As such, Applicants respectfully request that the Examiner withdraw the rejection.

d) With respect to the term "containing" in the definition of "heterocycle", Applicants have followed the Examiner's suggestion and amended the claims to set forth "having". As such, Applicants respectfully request that the Examiner withdraw the rejection.

In view of the foregoing amendments, Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 112, second paragraph.

II. REJECTION UNDER 35 U.S.C. § 112, first paragraph

Claims 1-16 were rejected under 35 U.S.C. §112, first paragraph, as allegedly being non-enabled for the term "prodrug derivative".

In an earnest effort to advance prosecution of the application, Applicants have amended the claims to delete the term. As such, Applicants respectfully request that the Examiner withdraw the rejection.

Claims 14-15 were rejected under 35 U.S.C. §112, first paragraph, as allegedly being non-enabled for preventing a condition...characterized by undesired thrombosis. In response, Applicants respectfully traverse the rejection.

Applicants respectfully point out that the proper standard for determining whether the claims are adequately enabled is whether undue experimentation is required by one skilled in the art to practice the invention. The analysis includes consideration of

factors such as the amount of guidance provided in the application and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, the claims are adequately enabled for treating the various conditions and indication set forth in claims 14-15, as one of ordinary skill in the art can practice the claimed invention without undue experimentation. As set out in *Wands*, “*a considerable* amount of experimentation is permissible, if it is merely *routine*, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should precede.” *In re Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982) (Emphasis added).

Clearly, in the instant application, the amount of experimentation is not undue as the specification gives adequate guidance. In this respect, the Examiner’s attention is respectfully directed to page 32, lines 13-17 of the present specification, wherein it teaches:

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Specific assays both *in vivo* and *in vitro*, to teach the biological efficacy are set forth in detail on page 41, line 24, continuing to the top of page 43. For example, amidolytic assays for determining protease inhibition activity has been described. These assays include, factor Xa and thrombin assays as well as prothrombinase inhibition assays.

In addition, the antithrombotic efficacy of the compounds was assayed in a rabbit model of venous thrombosis, using a rabbit deep vein thrombosis model as described by Hollenbach, S. *et al.*, *Thromb. Haemost.* 71, 357-362 (1994), wherein the *in-vivo* antithrombotic activity of the test compounds was determined.

Further, guidance is given in the biological data table set forth on page 46. As tabulated therein, 19 compounds were tested with a battery of biological assay. Based on the evidence regarding the detailed guidance set forth above, the specification at the time the application was filed, would have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

Moreover, Applicants assert that the number of working examples disclosed in the specification is sufficient to enable the full scope of the claims. Applicants are not required to disclose every type of indications within "undesired thrombosis". For example, in *In re Angstadt*, the court decided that Applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art" and that "the disclosure of forty working examples sufficiently described the subject matter of claims directed to a generic process." 537 F.2d at 502-03, 190 USPQ at 218. As such, if Applicants show efficacy for the treatment of undesired thrombosis, such as with a factor Xa assay, a thrombin assay as well as prothrombinase inhibition assay, they are entitled to sub-indications within such indication.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

III. REJECTION UNDER 35 U.S.C. 102(a)

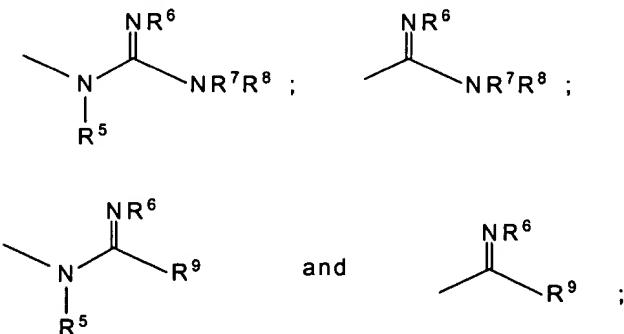
Claims 1-2 and 13-16 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by WO 99/50254 ("Dudley *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

"To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter" (see, *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996)).

Applicants have amended the structure in claim 1 to set forth quinolone derivatives. Applicants note that in no instance does Dudley *et al.* teach or suggest

quinolone derivatives *i.e.*, when "X" of the present Formula I is CR¹². As such, these derivatives are neither anticipated nor rendered obvious in view of Dudley *et al.*

Applicants have amended claim 2 to set forth quinoxalone derivatives, wherein "A" in Formula I, is a member selected from the following:



and Z is a member selected from the group of C₁₋₈alkyl, C₃₋₈cycloalkyl, and a five to ten membered heterocyclic ring system having 1-4 heteroatoms selected from the group consisting of N, O and S;

D is a member selected from the group of a direct link, -CH₂-, -O-, -N(R²)-, -C(=O)-, -S-, -SO₂-, -SO₂-N(R²)-, -N(R²)-SO₂-, -OC(=O)-, -C(=O)O-, -C(=O)-N(R²)- and -N(R²)-C(=O)-, provided that when Z is C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈carbocyclic aryl, then D is -O-, or -N(R²)-. The other variables have not been changed. This embodiment is not taught, suggested or disclosed in Dudley *et al.* As such, the instant invention is neither anticipated or rendered obvious in view of the cited art.

As such, Applicants respectfully request that the Examiner withdraw the rejection.

IV. CONCLUSION

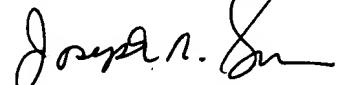
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Bing-Yang Zhu *et al.*
Application No.: 09/773,374
Page 21

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925.472.5000.

Respectfully submitted,

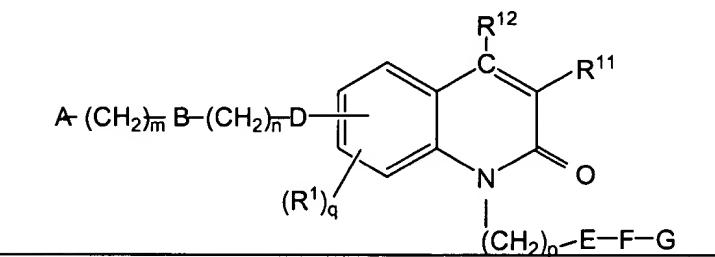
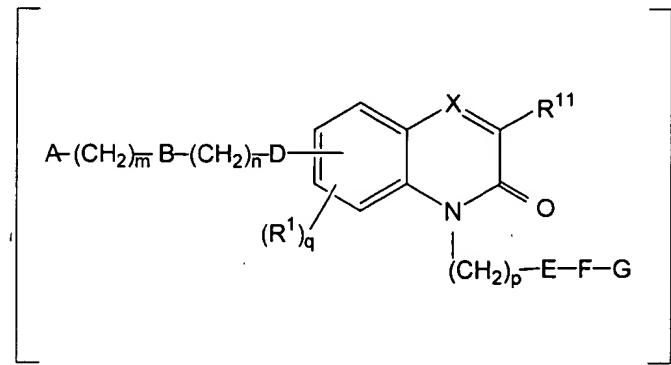


Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: (415) 576-0300
JS:js
WC 9047272 v1

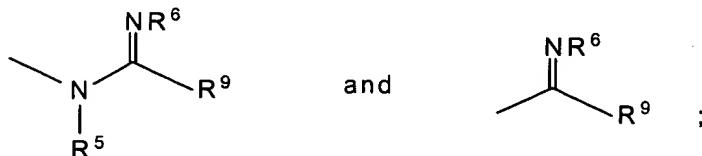
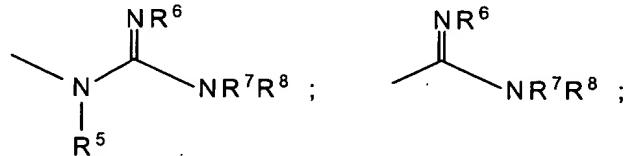
VERSION WITH MARKINGS TO SHOW CHANGES MADE in Amst A

1 1. (Amended) A compound of having the following formula:



wherein:

6 A is a member selected from the group consisting of: R², -NR³R⁴, -C(=O)NR³R⁴,



9 where R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from the group consisting of H, -OH, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, a five to ten membered heterocyclic ring system [containing] having 1-4

10 heteroatoms selected from the group consisting of N, O and S; and C₁₋₆alkylheterocyclic
11 ring system having in the ring system 5 to 10 atoms with 1 to 4 of such atoms being
12 selected from the group consisting of N, O and S; where R⁶ taken with either of R⁷ and
13 R⁸, and/or R⁷ taken with R⁸, can each form a 5 to 6 membered heterocyclic ring
14 [containing] having from 1 to 4 atoms selected from the group consisting of N, O and S;

15 m is an integer from 0-3;

16 Z is a member selected from the group consisting of a direct link, C₁₋₈alkyl,
17 C₃₋₈cycloalkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈carbocyclic aryl, or a five to ten membered
18 heterocyclic ring system [containing] having 1-4 heteroatoms selected from the group
19 consisting of N, O and S;

20 n is an integer from 0-3;

21 D is a member selected from the group consisting of a direct link, -CH₂-, -O-,
22 -N(R²)-, -C(=O)-, -S-, -SO₂-, -SO₂-N(R²)-, -N(R²)-SO₂-, -OC(=O)-, -C(=O)O-,
23 -C(=O)-N(R²)- and -N(R²)-C(=O)-;

24 R¹ is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈
25 alkynyl, C₃₋₈cycloalkyl, halogen, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH,
26 C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, -CN, -NO₂, [C₀₋₈alkyl-OH], C_{1-C₆alkyl-OH}, C₀₋₈alkyl-SH,
27 -C(=O)NR²R³, -O-R² and -O-C(=O)R², an unsubstituted amino group, a mono- or
28 di-substituted amino group, wherein the substituted amino groups are independently
29 substituted by at least one member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈
30 alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, polyhaloalkyl, -SO₂R², C₀₋₈alkyl-C(=O)OH and
31 C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, where R² and R³ is as described above;

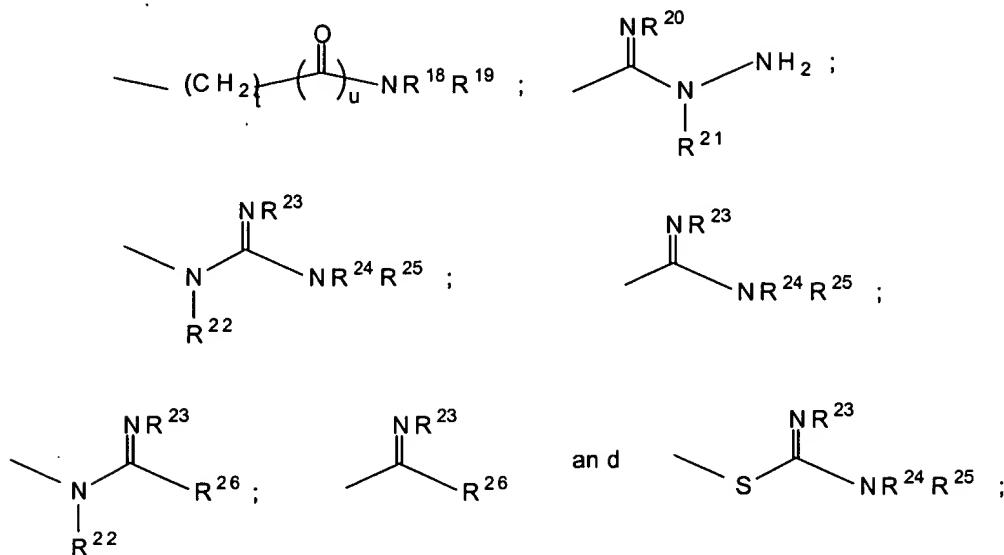
32 q is an integer from 0-3;

33 [X is N or -CR¹²];

34 R¹¹ and R¹² are independently a member selected from the group consisting of H,
35 C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, C₁₋₆alkylaryl,

36 $\text{C}_{1-6}\text{alkyl-C}_{3-8}\text{cycloalkyl, -O-R}^2$, $-\text{O-C(=O)R}^2$, $-\text{C}_{1-8}\text{alkyl-O-R}^{10}$, $-\text{C}_{1-8}\text{alkyl-O-C(=O)R}^{10}$,
37 $-\text{C}_{1-8}\text{alkyl-C(=O)OR}^{10}$, $-\text{C}_{1-8}\text{alkyl-O-C(=O)OR}^{10}$, $-\text{C}_{1-8}\text{alkyl-C(=O)NR}^{10}\text{R}^{10}$,
38 $-\text{C}_{1-8}\text{alkyl-NR}^{10}\text{R}^{10}$, $-\text{C}_{1-8}\text{alkyl-NR}^{10}\text{C(=O)R}^{10}$, $-\text{SR}^{10}$, where R^2 is as described above and
39 R^{10} is a member selected from the group consisting of H, $\text{C}_{1-8}\text{alkyl}$, $\text{C}_{2-8}\text{alkenyl}$, C_{2-8}
40 alkynyl , and wherein when two R^{10} groups are present they may be taken together to
41 form a saturated or unsaturated ring with the atom to which they are both attached;
42 p is an integer from 0-3;
43 E is a member selected from the group consisting of a direct link, $-\text{O-}$, $-\text{N}(-\text{R}^{11})-$,
44 where R^{11} is as set forth above, phenylene, a bivalent 5 to 12 member heteroaryl group
45 [containing] having 1 to 4 heteroatoms selected from the group consisting of N, O and S,
46 and a five to ten membered non-aromatic bivalent heterocyclic ring system [containing]
47 having 1-4 heteroatoms selected from the group consisting of N, O and S, wherein said
48 heteroaryl and said non-aromatic heterocyclic ring structure may be independently
49 substituted by from 0 to 5 R^{14} groups;
50 J is a member selected from the group consisting of a direct link, a bivalent
51 $\text{C}_{3-8}\text{cycloalkyl}$ group, phenylene, a 5 to 12 member bivalent heteroaryl group
52 [containing] having 1 to 4 heteroatoms selected from the group consisting of N, O and S,
53 and a five to ten membered non-aromatic bivalent heterocyclic ring system [containing]
54 having 1-4 heteroatoms selected from the group consisting of N, O and S wherein said
55 heteroaryl and said non-aromatic heterocyclic ring structure may be independently
56 substituted by from 0 to 5 R^{14} groups;
57 each R^{14} group is a member selected from the group consisting of H, $\text{C}_{1-8}\text{alkyl}$, C_{2-8}
58 alkenyl , $\text{C}_{2-8}\text{alkynyl}$, $\text{C}_{3-8}\text{cycloalkyl}$, halogen, polyhaloalkyl, $\text{C}_{0-8}\text{alkyl-C(=O)OH}$,
59 $\text{C}_{0-8}\text{alkyl-C(=O)O-C}_{1-8}\text{alkyl}$, $-\text{CN}$, $-\text{NO}_2$, [\text{C}_{0-8}\text{alkyl-OH}] $\text{C}_{1-C_6}\text{alkyl-OH}$, $\text{C}_{0-8}\text{alkyl-SH}$,
60 $-\text{O-R}^2$ and $-\text{O-C(=O)R}^2$, an unsubstituted amino group, a mono- or di-substituted amino
61 group, wherein the substituted amino groups are independently substituted by at least one
62 member selected from the group consisting of H, $\text{C}_{1-8}\text{alkyl}$, $\text{C}_{2-8}\text{alkenyl}$, $\text{C}_{2-8}\text{alkynyl}$,
63 $\text{C}_{3-8}\text{cycloalkyl}$, polyhaloalkyl, $\text{C}_{0-8}\text{alkyl-C(=O)OH}$ and $\text{C}_{0-8}\text{alkyl-C(=O)O-C}_{1-8}\text{alkyl}$;

64 G is a member selected from the group consisting of: H; -CN; -OR¹⁷;



65 wherein

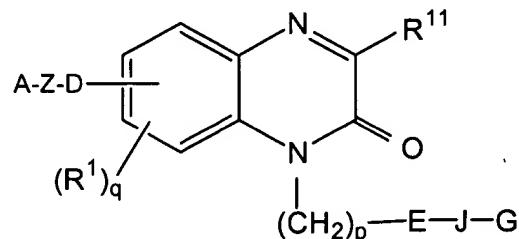
66 t is an integer from 0 to 6,

67 u is the integer 0 or 1, and R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵ and R²⁶ are
68 independently selected from the group consisting of H, -OH, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl,
69 C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, a five to ten membered heterocyclic ring
70 system [containing] having 1-4 heteroatoms selected from the group consisting of N, O
71 and S; and C₁₋₆alkylheterocyclic ring system having in the ring system 5 to 10 atoms with
72 1 to 4 of such atoms being selected from the group consisting of N, O and S; where [r¹⁸]
73 R¹⁸ taken with R¹⁹, R²² taken with either of R²⁴ and R²⁵, and R²⁴ taken with R²⁵, can each
74 independently form a 5 to 6 membered heterocyclic ring [containing] having from 1 to 4
75 atoms selected from the group consisting of N, O and S;

76 with the proviso that when G is H, -CN, -OR¹⁷, either E or J must contain at least
77 one N atom;

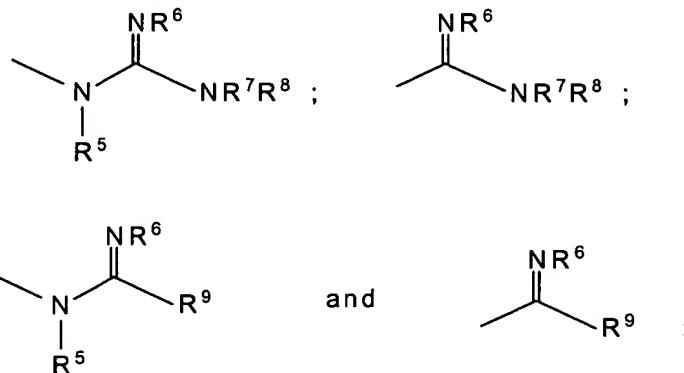
78 [and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
79 prodrug derivatives thereof] or a pharmaceutically acceptable diastereomer, salt,
80 hydrate, and solvate thereof.

1 2. (Amended) A compound of formula II:



2

3 A is a member selected from the group consisting of: [R², -NR³R⁴,
4 -C(=O)NR³R⁴,]



5 6 where [R², R³, R⁴,] R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from the group
7 consisting of H, -OH, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic
8 aryl, a five to ten membered heterocyclic ring system [containing] having 1-4
9 heteroatoms selected from the group consisting of N, O and S; and C₁₋₆alkylheterocyclic
10 ring system having in the ring system 5 to 10 atoms with 1 to 4 of such atoms being
11 selected from the group consisting of N, O and S; where [r⁶] R⁶ taken with either of R⁷
12 and R⁸, and/or R⁷ taken with R⁸, can each form a 5 to 6 membered heterocyclic ring
13 [containing] having from 1 to 4 atoms selected from the group consisting of N, O and S;

14 Z is a member selected from the group consisting of [a direct link,] C₁₋₈alkyl,

15 C_{3-8} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} carbocyclic aryl, or a five to ten membered
16 heterocyclic ring system [containing] having 1-4 heteroatoms selected from the group
17 consisting of N, O and S;

18 D is a member selected from the group consisting of a direct link, $-CH_2-$, $-O-$,
19 $-N(R^2)-$, $-C(=O)-$, $-S-$, $-SO_2-$, $-SO_2-N(R^2)-$, $-N(R^2)-SO_2-$, $-OC(=O)-$, $-C(=O)O-$,
20 $-C(=O)-N(R^2)-$ and $-N(R^2)-C(=O)-$ provided that when Z is C_{1-8} alkyl, C_{2-8} alkenyl,
21 C_{2-8} alkynyl, C_{1-8} carbocyclic aryl, then D is $-O-$, or $-N(R^2)-$;

22 R^1 is a member selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, halogen, polyhaloalkyl, C_{0-8} alkyl- $C(=O)OH$,
23 C_{0-8} alkyl- $C(=O)O-C_{1-8}$ alkyl, -CN, $-NO_2$, $[C_{0-8}$ alkyl-OH,] C_{1-C_6} alkyl-OH, C_{0-8} alkyl-SH,
24 $-C(=O)NR^2R^3$, $-O-R^2$ and $-O-C(=O)R^2$, an unsubstituted amino group, a mono- or
25 di-substituted amino group, wherein the substituted amino groups are independently
26 substituted by at least one member selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, polyhaloalkyl, $-SO_2R^2$, C_{0-8} alkyl- $C(=O)OH$ and
27 C_{0-8} alkyl- $C(=O)O-C_{1-8}$ alkyl, [where R^2 and R^3 is as described above];

30 R^2 , R^3 are independently selected from the group consisting of H, -OH, C_{1-8} alkyl,
31 C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{6-12} carbocyclic aryl, a five to ten membered
32 heterocyclic ring system having 1-4 heteroatoms selected from the group consisting of N,
33 O and S; and C_{1-6} alkylheterocyclic ring system having in the ring system 5 to 10 atoms
34 with 1 to 4 of such atoms being selected from the group consisting of N, O and S;

35 q is an integer from 0-3;

36 R^{11} is independently a member selected from the group consisting of H, C_{1-8} alkyl,
37 C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{6-12} carbocyclic aryl, C_{1-6} alkylaryl,
38 C_{1-6} alkyl- C_{3-8} cycloalkyl, $-O-R^2$, $-O-C(=O)R^2$, $-C_{1-8}$ alkyl- $O-R^{10}$, $-C_{1-8}$ alkyl- $O-C(=O)R^{10}$,
39 $-C_{1-8}$ alkyl- $C(=O)OR^{10}$, $-C_{1-8}$ alkyl- $O-C(=O)OR^{10}$, $-C_{1-8}$ alkyl- $C(=O)NR^{10}R^{10}$,
40 $-C_{1-8}$ alkyl- $NR^{10}R^{10}$, $-C_{1-8}$ alkyl- $NR^{10}C(=O)R^{10}$, $-SR^{10}$, where R^2 is as described above and

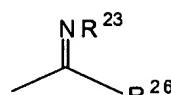
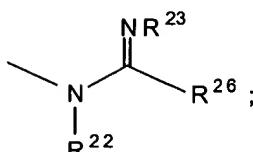
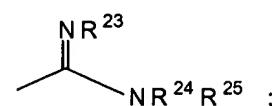
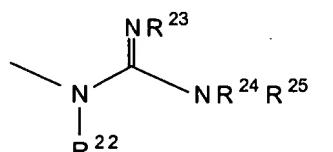
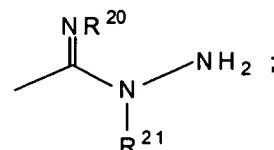
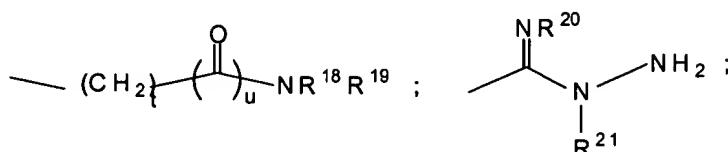
41 R^{10} is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, and wherein when two R^{10} groups are present they may be taken together to
42 form a saturated or unsaturated ring with the atom to which they are both attached;
43 p is an integer from 0-2;

45 E is a member selected from the group consisting of a direct link, -O-, -N(-R¹¹)-,
46 where R¹¹ is as set forth above, phenylene, a bivalent 5 to 12 member heteroaryl group
47 [containing] having 1 to 4 heteroatoms selected from the group consisting of N, O and S,
48 and a five to ten membered non-aromatic bivalent heterocyclic ring system [containing]
49 having 1-4 heteroatoms selected from the group consisting of N, O and S, wherein said
50 heteroaryl and said non-aromatic heterocyclic ring structure may be independently
51 substituted by from 0 to 5 R¹⁴ groups;

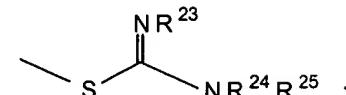
52 J is a member selected from the group consisting of a direct link, a bivalent
53 C₃₋₈cycloalkyl group, phenylene, a 5 to 12 member bivalent heteroaryl group
54 [containing] having 1 to 4 heteroatoms selected from the group consisting of N, O and S,
55 and a five to ten membered non-aromatic bivalent heterocyclic ring system [containing]
56 having 1-4 heteroatoms selected from the group consisting of N, O and S wherein said
57 heteroaryl and said non-aromatic heterocyclic ring structure may be independently
58 substituted by from 0 to 5 R¹⁴ groups;

59 each R¹⁴ group is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, halogen, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH, C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, -CN, -NO₂, [C₀₋₈alkyl-OH,] C_{1-C₆}alkyl-OH, C₀₋₈alkyl-SH, -O-R² and -O-C(=O)R², an unsubstituted amino group, a mono- or di-substituted amino group, wherein the substituted amino groups are independently substituted by at least one member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH and C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl;

66 G is a member selected from the group consisting of: H; -CN; -OR¹⁷;



and



67 wherein

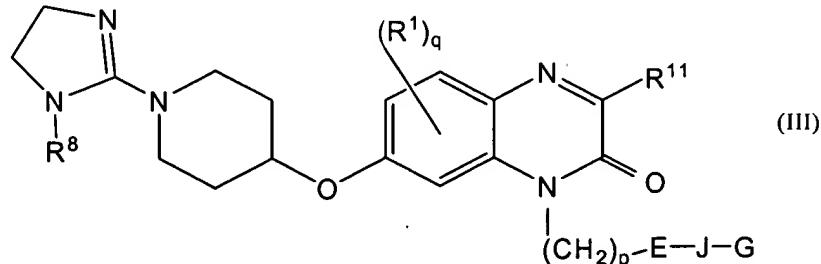
68 t is an integer from 0 to 6,

69 u is the integer 0 or 1, and R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵ and R²⁶ are
70 independently selected from the group consisting of H, -OH, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, a five to ten membered heterocyclic ring
71 system [containing] having 1-4 heteroatoms selected from the group consisting of N, O
72 and S; and C₁₋₆alkylheterocyclic ring system having in the ring system 5 to 10 atoms with
73 1 to 4 of such atoms being selected from the group consisting of N, O and S; where [r¹⁸]
74 R¹⁸ taken with R¹⁹, R²² taken with either of R²⁴ and R²⁵, and R²⁴ taken with R²⁵, can each
75 independently form a 5 to 6 membered heterocyclic ring [containing] having from 1 to 4
76 atoms selected from the group consisting of N, O and S;
77 atoms selected from the group consisting of N, O and S;

78 with the proviso that when G is H, -CN, -OR¹⁷, either E or J must contain at least
79 one N atom;

80 **[and all pharmaceutically acceptable isomers, salts, hydrates, solvates and**
81 **prodrug derivatives thereof] or a pharmaceutically acceptable diastereomer, salt,**
82 **hydrate, and solvate thereof.**

1 5. (Amended) A compound of formula III:



2

3

4

5 wherein:

6 R⁸ is selected from the group consisting of H, -OH, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, a five to ten membered heterocyclic ring system [containing] having 1-4 heteroatoms selected from the group consisting of N, O and S; and C₁₋₆alkylheterocyclic ring system having in the ring system 5 to 10 atoms with 1 to 4 of such atoms being selected from the group consisting of N, O and S;

11 R¹ is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, halogen, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH, C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, -CN, -NO₂, [C₀₋₈alkyl-OH,] C_{1-C₆}alkyl-OH, C₀₋₈alkyl-SH, -C(=O)NR²R³, -O-R² and -O-C(=O)R², an unsubstituted amino group, a mono- or di-substituted amino group, wherein the substituted amino groups are independently substituted by at least one member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, polyhaloalkyl, -SO₂R², C₀₋₈alkyl-C(=O)OH and C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, where R² and R³ is as described above;

19 R² is selected from the group consisting of H, -OH, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, a five to ten membered heterocyclic ring

21 system **[containing]** having 1-4 heteroatoms selected from the group consisting of N, O
22 and S; and C₁₋₆alkylheterocyclic ring system having in the ring system 5 to 10 atoms with
23 1 to 4 of such atoms being selected from the group consisting of N, O and S;
24 q is 0-3;

25 R¹¹ is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl,
26 C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, C₁₋₆alkylaryl, C₁₋₆alkyl-C₃₋₈cycloalkyl,
27 -O-R², -O-C(=O)R², -C₁₋₈alkyl-O-R¹⁰, -C₁₋₈alkyl-O-C(=O)R¹⁰, -C₁₋₈alkyl-C(=O)OR¹⁰,
28 -C₁₋₈alkyl-O-C(=O)OR¹⁰, -C₁₋₈alkyl-C(=O)NR¹⁰R¹⁰, -C₁₋₈alkyl-NR¹⁰R¹⁰,
29 -C₁₋₈alkyl-NR¹⁰C(=O)R¹⁰, -SR¹⁰, where R² is as described above and R¹⁰ is a member
30 selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, and wherein
31 when two R¹⁰ groups are present they may be taken together to form a saturated or
32 unsaturated ring with the atom to which they are both attached;

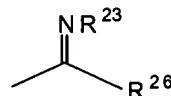
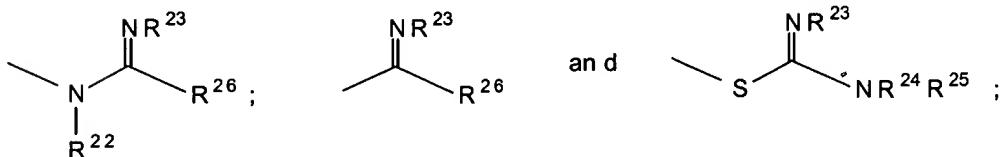
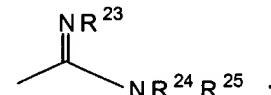
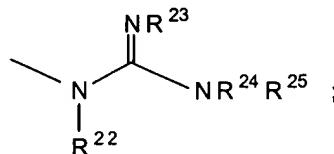
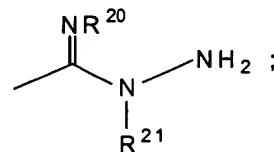
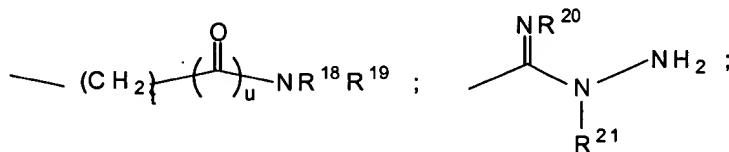
33 p is an integer from 0-2;

34 E is a member selected from the group consisting of a direct link, -O-, -N(-R¹¹)-,
35 where R¹¹ is as set forth above, phenylene, a bivalent 5 to 12 member heteroaryl group
36 **[containing]** having 1 to 4 heteroatoms selected from the group consisting of N, O and S,
37 and a five to ten membered non-aromatic bivalent heterocyclic ring system **[containing]**
38 having 1-4 heteroatoms selected from the group consisting of N, O and S, wherein said
39 heteroaryl and said non-aromatic heterocyclic ring structure may be independently
40 substituted by from 0 to 5 R¹⁴ groups;

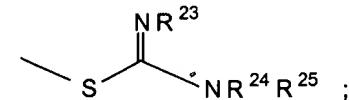
41 J is a member selected from the group consisting of a direct link, a bivalent
42 C₃₋₈cycloalkyl group, phenylene, a 5 to 12 member bivalent heteroaryl group
43 **[containing]** having 1 to 4 heteroatoms selected from the group consisting of N, O and S,
44 and a five to ten membered non-aromatic bivalent heterocyclic ring system **[containing]**
45 having 1-4 heteroatoms selected from the group consisting of N, O and S wherein said
46 heteroaryl and said non-aromatic heterocyclic ring structure may be independently
47 substituted by from 0 to 5 R¹⁴ groups;

48 each R¹⁴ group is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, halogen, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH, C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, -CN, -NO₂, [C₀₋₈alkyl-OH], C_{1-C₆}alkyl-OH, C₀₋₈alkyl-SH, -O-R² and -O-C(=O)R², an unsubstituted amino group, a mono- or di-substituted amino group, wherein the substituted amino groups are independently substituted by at least one member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH and C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl;

55 G is a member selected from the group consisting of: H; -CN; -OR¹⁷;



and



56 wherein

57 t is an integer from 0 to 6,

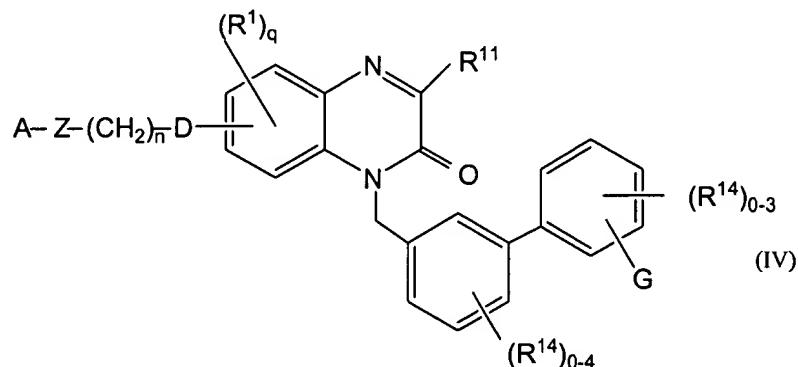
58 u is the integer 0 or 1, and R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵ and R²⁶ are independently selected from the group consisting of H, -OH, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, a five to ten membered heterocyclic ring system [containing] having 1-4 heteroatoms selected from the group consisting of N, O and S; and C₁₋₆alkylheterocyclic ring system having in the ring system 5 to 10 atoms with 1 to 4 of such atoms being selected from the group consisting of N, O and S; where [r¹⁸]

64 R¹⁸ taken with R¹⁹, R²² taken with either of R²⁴ and R²⁵, and R²⁴ taken with R²⁵, can each
65 independently form a 5 to 6 membered heterocyclic ring [containing] having from 1 to 4
66 atoms selected from the group consisting of N, O and S;

67 with the proviso that when G is H, -CN, -OR¹⁷, either E or J must contain at least
68 one N atom;

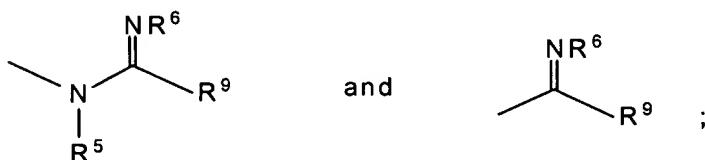
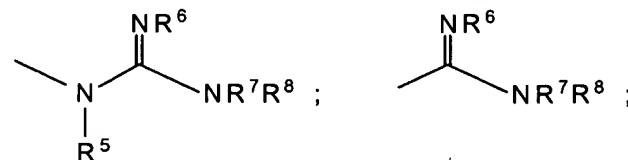
69 [and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
70 prodrug derivatives thereof] or a pharmaceutically acceptable diastereomer, salt,
71 hydrate, and solvate thereof.

1 9. A compound of formula IV:



3 wherein:

4 A is a member selected from the group consisting of: R^2 , $-NR^3R^4$, $-C(=O)NR^3R^4$,



6 where R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from the group
 7 consisting of H, -OH, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{6-12} carbocyclic

8 aryl, a five to ten membered heterocyclic ring system **[containing]** having 1-4
9 heteroatoms selected from the group consisting of N, O and S; and C₁₋₆alkylheterocyclic
10 ring system having in the ring system 5 to 10 atoms with 1 to 4 of such atoms being
11 selected from the group consisting of N, O and S; where [r⁶] R⁶ taken with either of R⁷
12 and R⁸, and/or R⁷ taken with R⁸, can each form a 5 to 6 membered heterocyclic ring
13 **[containing]** having from 1 to 4 atoms selected from the group consisting of N, O and S;

14 Z is a member selected from the group consisting of a direct link, C₁₋₈alkyl,
15 C₃₋₈cycloalkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈carbocyclic aryl, or a five to ten membered
16 heterocyclic ring system **[containing]** having 1-4 heteroatoms selected from the group
17 consisting of N, O and S;

18 n is 0-3;

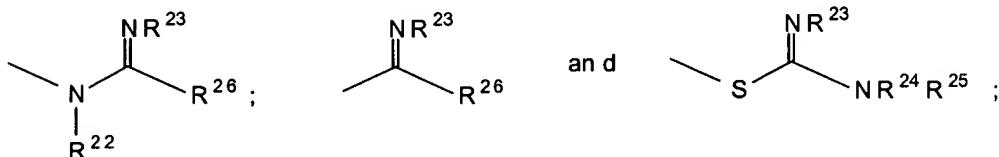
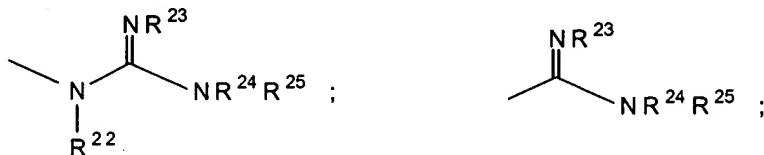
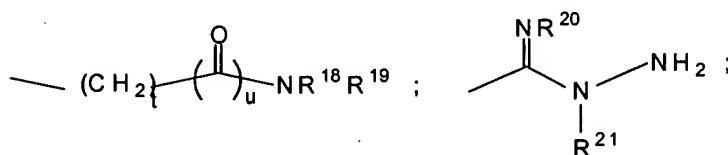
19 D is a member selected from the group consisting of: -CH₂-, -O-, -N R², -C(=O)-,
20 -S-, -SO₂-, -SO₂-NR², -NR²-SO₂, -OC(=O)-, -C(=O)NR², and -NR²-C(=O)-;

21 R¹ and R¹⁴ are independently a member selected from the group consisting of H,
22 C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, halogen, polyhaloalkyl,
23 C₀₋₈alkyl-C(=O)OH, C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, -CN, -NO₂, **[C₀₋₈alkyl-OH,]** C₁₋
24 C₆alkyl-OH, C₀₋₈alkyl-SH, -O-R² and -O-C(=O)R², an unsubstituted amino group, a
25 mono- or di-substituted amino group, wherein the substituted amino groups are
26 independently substituted by at least one member selected from the group consisting of
27 H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH
28 and C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl;

29 q is 0-3;

30 R¹¹ is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl,
31 C₂₋₈alkynyl, C₃₋₈cycloalkyl, C₆₋₁₂carbocyclic aryl, C₁₋₆alkylaryl, C₁₋₆alkyl-C₃₋₈cycloalkyl,
32 -O-R², -O-C(=O)R², -C₁₋₈alkyl-O-R¹⁰, -C₁₋₈alkyl-O-C(=O)R¹⁰, -C₁₋₈alkyl-C(=O)OR¹⁰,
33 -C₁₋₈alkyl-O-C(=O)OR¹⁰, -C₁₋₈alkyl-C(=O)NR¹⁰R¹⁰, -C₁₋₈alkyl-NR¹⁰R¹⁰,
34 -C₁₋₈alkyl-NR¹⁰C(=O)R¹⁰, -SR¹⁰, where R² is as described above and R¹⁰ is a member

35 selected from the group consisting of H, C₁-alkyl, C₂-alkenyl, C₂-alkynyl, and wherein
36 when two R¹⁰ groups are present they may be taken together to form a saturated or
37 unsaturated ring with the atom to which they are both attached;
38 G is a member selected from the group consisting of: H; -CN; -OR¹⁷;



39 wherein

40 t is an integer from 0 to 6,

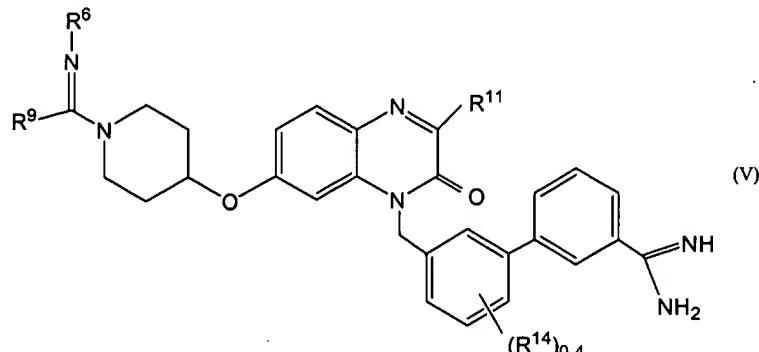
41 u is the integer 0 or 1, and R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵ and R²⁶ are
42 independently selected from the group consisting of H, -OH, C₁-alkyl, C₂-alkenyl, C₂-
43 alkynyl, C₃-cycloalkyl, C₆-12 carbocyclic aryl, a five to ten membered heterocyclic ring
44 system **[containing]** having 1-4 heteroatoms selected from the group consisting of N, O
45 and S; and C₁-6 alkylheterocyclic ring system having in the ring system 5 to 10 atoms with
46 1 to 4 of such atoms being selected from the group consisting of N, O and S; where **[r^{18]}**
47 R¹⁸ taken with R¹⁹, R²² taken with either of R²⁴ and R²⁵, and R²⁴ taken with R²⁵, can each
48 independently form a 5 to 6 membered heterocyclic ring **[containing]** having from 1 to 4
49 atoms selected from the group consisting of N, O and S;

50 with the proviso that when G is H, -CN, -OR¹⁷, either E or J must contain at least

51 one N atom;

52 [and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
53 prodrug derivatives thereof] or a pharmaceutically acceptable diastereomer, salt,
54 hydrate, and solvate thereof.

1 11. A compound of formula V:



2

3

4 wherein:

5 R^2 , R^6 , and R^9 are independently selected from the group consisting of H, -OH,
6 C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{6-12} carbocyclic aryl, a five to ten
7 membered heterocyclic ring system [containing] having 1-4 heteroatoms selected from
8 the group consisting of N, O and S; and C_{1-6} alkylheterocyclic ring system having in the
9 ring system 5 to 10 atoms with 1 to 4 of such atoms being selected from the group
10 consisting of N, O and S;

11

12 R^{11} is independently a member selected from the group consisting of H,
13 C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{6-12} carbocyclic aryl, C_{1-6} alkylaryl,
14 C_{1-6} alkyl- C_{3-8} cycloalkyl, -O- R^2 , -O-C(=O) R^2 , - C_{1-8} alkyl-O- R^{10} , - C_{1-8} alkyl-O-C(=O) R^{10} ,
15 - C_{1-8} alkyl-C(=O)OR¹⁰, - C_{1-8} alkyl-O-C(=O)OR¹⁰, - C_{1-8} alkyl-C(=O)NR¹⁰R¹⁰,
16 - C_{1-8} alkyl-NR¹⁰R¹⁰, - C_{1-8} alkyl-NR¹⁰C(=O)R¹⁰, -SR¹⁰, where R^2 is as described above and
17 R^{10} is a member selected from the group consisting of H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8}
18 alkynyl, and wherein when two R^{10} groups are present they may be taken together to

19 form a saturated or unsaturated ring with the atom to which they are both attached;
20
21 each R¹⁴ group is a member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, halogen, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH, C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl, -CN, -NO₂, [C₀₋₈alkyl-OH], C_{1-C₆}alkyl-OH, C₀₋₈alkyl-SH, -O-R² and -O-C(=O)R², an unsubstituted amino group, a mono- or di-substituted amino group, wherein the substituted amino groups are independently substituted by at least one member selected from the group consisting of H, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, polyhaloalkyl, C₀₋₈alkyl-C(=O)OH and C₀₋₈alkyl-C(=O)O-C₁₋₈alkyl;
28 [and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
29 prodrug derivatives thereof] or a pharmaceutically acceptable diastereomer, salt,
30 hydrate, and solvate thereof.